



THE VALUE OF A BD INTEGRATED SYSTEM FOR COMBINATION PRODUCTS

The growing complexity and regulatory rigour of combination products has called for increasingly innovative delivery devices. In this article, Theresa Bankston, PhD, Director, Technical Services looks at the advantages of using an integrated system for these drug-device combination products rather than sourcing components from different suppliers. As well as avoiding problems such as breakage and incompatibility, integrated products can offer solutions at every interface between the drug, container and delivery device and save significant amounts of time and money.

The number of biological therapies in development to treat chronic diseases has risen steadily over the years. The fact that many of these therapies are designed for home delivery by patients or caregivers via subcutaneous injection, combined with the increasing complexity of longer acting formulations, larger injection volumes and longer injection durations, has raised the bar for seamless injection delivery technology. Patients today receive these drugs inside prefilled injection devices, together called combination products. These combination products include auto-injectors, wearable injectors, and prefilled syringes.

To bring a drug-device combination product to market, pharmaceutical companies must select and assemble multiple components that work together optimally to deliver the drug formulation safely and effectively. These components include, but are not limited to:

- A primary container consisting of a syringe barrel, stopper, plunger rod and backstop
- A secondary delivery system such as an auto-injector or wearable injector
- An add-on needlestick safety guard.

Drug makers and their contract manufacturing partners have the option of sourcing these components from a variety of suppliers. However, pharmaceutical companies who purchase components separately take on additional risks that can be significantly reduced by selecting an integrated system instead.

RISKS OF USING SEPARATE COMPONENTS

Broadly, the risks addressed by system integration include the delivery system not functioning as intended, such as primary container breakage, inconsistent



Dr Theresa Bankston
Director, Technical Services
T: +1 201 847 5237
E: theresa.bankston@bd.com

**BD Medical –
Pharmaceutical Systems**
1 Becton Drive
Franklin Lakes
NJ 07417
United States

www.bd.com

“For combination products to perform most effectively, special attention must be paid to component interfaces throughout the product development and delivery process, from the early design phases to manufacturing strategy and execution.”

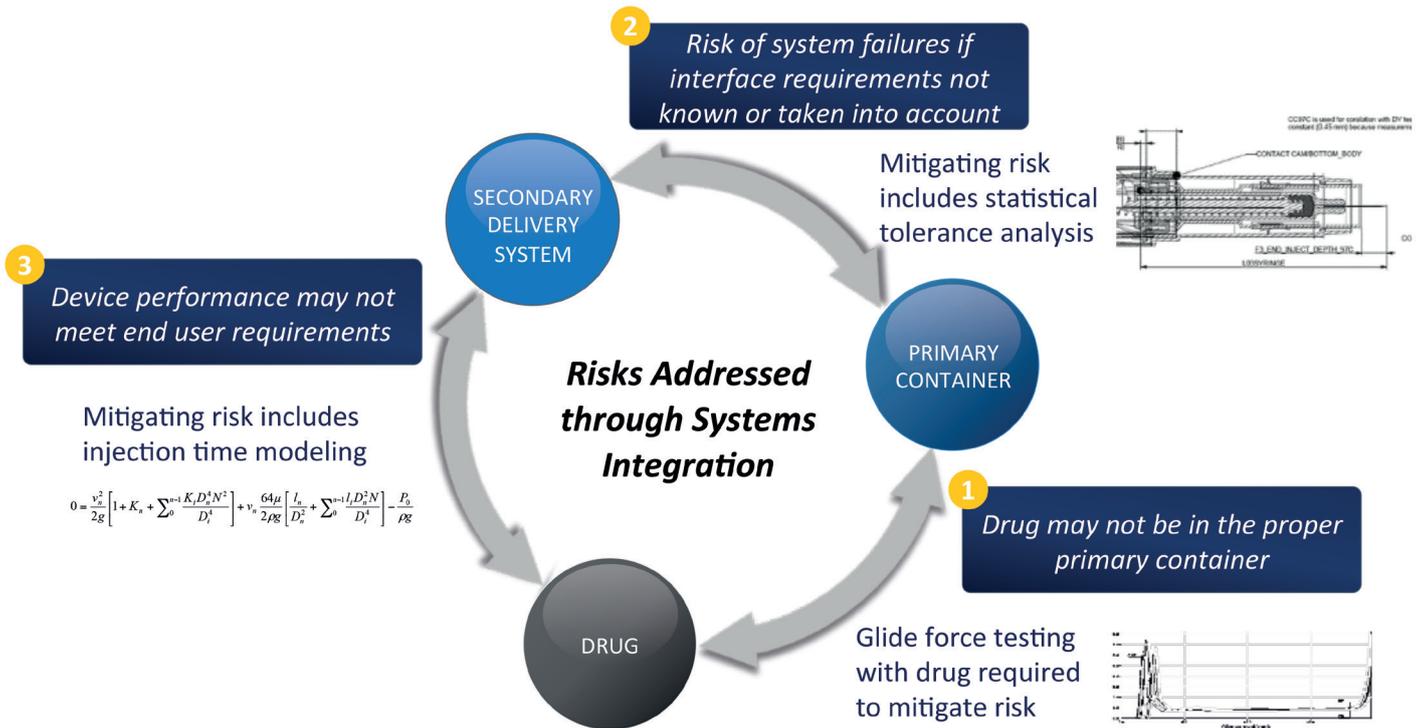


Figure 1: Risks addressed by well managed systems.

system performance and incompatibility with key container components (Figure 1). When realised, these risks bring issues such as an increase in project management complexity and time, a potential delay to launch and unforeseen problems post-launch, amongst others. Moreover, problems may not be revealed until late in development, or possibly after commercialisation when the combination product has already been manufactured in large quantities, and reached the hands of patients. Consequences can range from high scrap rates and waste during the filling or assembly process to a loss of costly drug and a delay of therapy in the care setting.

These risks and the costs associated with them, whilst real, may not be immediately obvious to the pharmaceutical company.

ADVANTAGES OF SYSTEM INTEGRATION

Assurance Through Expertise

For combination products to perform most effectively, special attention must be paid to component interfaces throughout the product development and delivery process, from the early design phases to manufacturing strategy and execution. BD is a leading provider of primary containers globally and offers secondary delivery systems, including needlestick safety systems, wearable injectors and auto-injectors, for a complete combination product solution.

Due to its legacy of developing and providing billions of prefillable syringes and components to the pharmaceutical industry every year, BD has the experience, analytical tools and lab test capabilities to optimise the components of combination products to operate cohesively. As a result, pharmaceutical companies can benefit from delivery system interfaces that have been properly managed well in advance of product assembly and launch.

BD designs its secondary delivery systems to integrate with the well established primary containers most pharmaceutical manufacturers are already accustomed to using in their auto-injectors, wearable injectors and safety systems. This not only provides convenience, but also enables more flexibility in device selection before manufacturers make downstream decisions about device features and functionality.

For example, BD integrates its best-in-class BD Hypak™, BD Neopak™ and cannula technologies into their self-injection systems, providing multi-platform flexibility across a range of dose volumes. BD’s wearable injector, BD Libertas™, is the leading model of BD systems integration, designed from the bottom up, with an array of proven BD components, including BD Neopak™ technology and cannula.

BD also offers a leading brand of passive needle guards through its BD UltraSafe Passive™ and BD Plus™ Needle Guards. Unlike most add-on safety devices, BD

UltraSafe Passive™ and BD Plus™ Passive Needle Guards are designed to work with BD prefillable syringes. “Because BD develops both components, we can test compatibility long before a pharmaceutical customer has the opportunity to test the components together with a specific drug,” said Sarah Baer, Global Strategic Marketing Leader.

“It’s widely known that BD offers world-class primary containers for combination product development. Our customers are also increasingly coming to understand our investment and full capabilities in delivering exceptional secondary delivery devices. They understand the benefits of working with BD to manage the increasingly complex combination product world,” added Bernard Egoyan, Vice-President BD Medical – Pharmaceutical Systems.

“The most significant time and cost savings come from avoiding potentially delayed launch timelines.”

Solutions at Each Interface

BD’s integrated systems offer solutions to the complexities of combination products at every interface between the drug, primary container and secondary delivery system. Consider a few examples of this:

- At the interface between the drug and primary container, BD leverages its expertise and capabilities in glide force testing to ensure the drug is in the appropriate primary container to meet the manufacturer's needs.
- Between the primary container and the device, BD provides statistical tolerance analysis to specify interface requirements that minimise the risk of system failures.
- Between the drug and secondary delivery system, BD employs injection time modelling to improve overall device performance.

THE VALUE OF INTEGRATION

Risk Mitigation

System integration provides value to pharmaceutical companies and patients at several levels. A well integrated system anticipates and mitigates system performance risks early in development. BD performs system validation and design verification testing on established reference systems, challenging system performance at the limits of process capability. The outputs of this process are provided in summary report documentation.

BD can also anticipate where problems can arise throughout the development process and how to troubleshoot them effectively. Because BD produces both primary and secondary systems, they have a unique appreciation of nuances in meeting ISO standards that can help customers.

Visibility across secondary system platforms results in product designs that reflect detailed component specifications to ensure system integration between BD prefillable syringes and BD secondary systems, both during development and after manufacturing scale-up through commercialisation. Internal experts share learnings from implementation experience across project teams. Moreover, quality commitment is maintained at the component and system (including primary container) level, which forces tighter specifications and reduced variability in system performance. This drives a high degree of accountability for BD, as the pharmaceutical sponsor can hold a single party accountable for performance of the total delivery system.

“BD creates and manufactures to specifications that are so tight, pharma can accurately predict performance and put components together successfully with less risk of waste,” explained Janice Adkins, Associate Director, Marketing.

Finally, BD conducts human factors engineering testing on its most advanced products across a range of representative users to confirm that the integrated devices are safe and user-friendly as a system. While pharmaceutical companies will conduct their own testing with the actual formulation, this early testing of the system increases confidence in the usability of the combined components and reduces the risk of unforeseen issues.

Time and Cost Savings

BD's system integration has been designed to facilitate significant time and cost savings. On a case by case basis BD provides data at the system level, incorporating the primary container, which creates a more readily usable format for the critical step of combination product registration filing. And as BD continuously improves their manufacturing processes and product designs the “fit” between primary and secondary containers is proactively verified and tracked, and potential problems are resolved to avoid performance issues that may ensue.

BD's leading primary container technology designed for biologic drugs, BD Neopak™, ensures a fit with many secondary systems, including BD handheld auto-injectors, wearable injectors and passive safety devices. This enhanced fit supports greater choice and flexibility for pharmaceutical companies to serve diverse patient groups, therapeutic areas and markets with the appropriate delivery format. Furthermore, a single prefillable syringe technology that integrates with a broad range of secondary delivery systems can minimise the costs associated with managing multiple component interfaces and suppliers.

The most significant time and cost savings come from avoiding potentially delayed launch timelines. BD's integrated approach is focused on ensuring that every system component, including the barrel,

Category	Products
Prefillable syringes	<ul style="list-style-type: none"> BD Neopak™ 2.25 mL Prefillable Syringe BD Neopak™ Prefillable Syringe BD Hypak™ for Biotech Prefillable Syringe
Safety systems	<ul style="list-style-type: none"> BD UltraSafe Plus™ 2.25 mL Passive Needle Guard BD UltraSafe Plus™ Passive Needle Guard
Auto-injectors	<ul style="list-style-type: none"> BD Intevia™ Disposable Auto-injector BD Physioject™ Disposable Auto-injector
Wearable injectors*	<ul style="list-style-type: none"> BD Libertas™ Wearable Injector

*Not commercially available.

Figure 2: The range of BD's fully integrated devices.



Figure 3: BD Physioject™ auto-injector.

stopper, needle, needle shield, primary container and secondary delivery system, functions cohesively. This approach is intended to develop a seamless delivery system that performs as designed and meets the rigorous regulatory requirements for safety, effectiveness, functionality and usability.

“BD ensures that our components will work together. There are no surprises that the primary container selected doesn’t work or fit perfectly with the device,” commented Justyna Dudaronek, Manager of Technical Services.

End-to-End Services Add Value

Based on BD’s experience in designing and integrating components into systems and extensive collaboration with drug developers, BD has developed a range of end-to-end services it offers to customers. These services are designed to help their pharmaceutical partners choose the correct components and system for their application, to assess and offer solutions to any potential challenges or sensitivities, and to help produce the necessary data packages needed to demonstrate the safety and performance of the integrated combination product. These include:

- Analytical and bioanalytical chemistry capabilities
- Formulation services
- Functional and performance testing
- Clinical/human factors consultancy
- Combination product documentation support and testing
- Process consultancy
- Regulatory customised support.



Figure 4: BD Intevia™ auto-injector.

For example, testing for performance feasibility may include *in vivo* testing, demonstrating that a range of injection volumes or flow rates is feasible. Combination product support occurs throughout the development process, from matching the right set of components with the formulation in Phases I and II, to validation testing of the system in Phases II and III.

Only BD offers this breadth of capabilities in combination with the entire system of components (Figure 2) to enable customers to anticipate and resolve challenges before they become issues from a system interference perspective.

BD’S FULLY-INTEGRATED DEVICES

Auto-Injectors

BD Physioject™ is a disposable auto-injector that fully integrates with the BD Neopak™ 1 mL glass prefilled syringe or the BD Hypak™ for biotech 1 mL glass prefilled syringe (Figure 3).

BD Intevia™ is an auto-injector platform technology specifically designed for high-viscosity drug delivery. BD Intevia™ supports biotech’s evolving needs for high dosages, whilst offering integration with BD Neopak™ technology and BD Hypak™ for biotech, offering manufacturers the flexibility to accommodate formulation changes (Figure 4).

Wearable Injector

BD Libertas™ is a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high viscosity biologics. It was purposefully designed to work as an integrated system with BD Neopak™ technology and fits within current manufacturing assembly technology, both providing high performance and prefilled convenience for patients (Figure 5).

Safety Systems

The BD UltraSafe™ family of products are add-on passive needle guards for prefilled glass syringes, offering versions for both cut flanges and small, round flanges. BD UltraSafe Passive™ and BD Plus™ Needle Guards are market-leading safety solutions for prefilled glass syringes. BD conducts a multi-phase set of compatibility tests to ensure primary container integration (Figure 6).



Figure 5: BD Libertas™ wearable injector.



Figure 6: BD UltraSafe Passive™ and BD Plus™ Needle Guards.

EXAMPLES OF CHALLENGES ADDRESSED WITH INTEGRATED SYSTEMS

Drawn from years of experience with customers, the following are examples of real-world challenges faced with non-integrated components from different suppliers (Figure 7) and the corresponding solutions offered by integrated systems – auto-injector examples used are BD Physioject™ and BD Intevia™.

Cap Removal Malfunction & Wasted Drug

Limitation of a non-integrated system: When patients remove the cap from an auto-injector, the rigid needle shield (RNS) may not always be pulled from the needle. The result could be an uncapping motion that damages the needle and the drug delivery device. In this case, the device becomes unusable and the patient may fail to receive

their important and expensive medication. For the pharmaceutical company this issue may produce complaints, drug wastage and negative quality perception. Although some companies may recognise this issue during development and may resolve it by switching to a different auto-injector, others may not observe it until after scale-up and launch.

Integrated system solution: With BD’s integrated auto-injectors, the caps are designed to integrate with and reliably remove the RNS so that the needle is not damaged. Knowing that even minor changes such as replacing mould tools can affect RNS dimensions, design and manufacturing updates are routinely and proactively assessed by BD for their impact to cap/RNS integration. BD designs for system performance to help manufacturers avoid project delays and post-launch issues.

“BD’s integrated systems offer a means to incorporate already existing world-class technologies with novel secondary delivery device solutions to provide complete products that meet the evolving needs of pharmaceutical manufacturers.”

Needle Extension Variability

Limitation of a non-integrated system: Needle extension (depth) is not always well-controlled or understood when the auto-injectors and prefillable syringes are combined. The range of specifications for each component can result in an unexpectedly wide variation when the tolerances are stacked.

As a result, unexpected clinical outcomes may occur when bridging from syringe injection to auto-injection. The implications of this issue are that pharmaceutical companies may have to repeat clinical studies or perhaps even re-design the auto-injector or prefillable syringe. Either case could result in product launch delays.

Integrated system solution: Injection depth was thoroughly characterised and controlled during the development of BD Physioject™ and BD Intevia™, through close work with

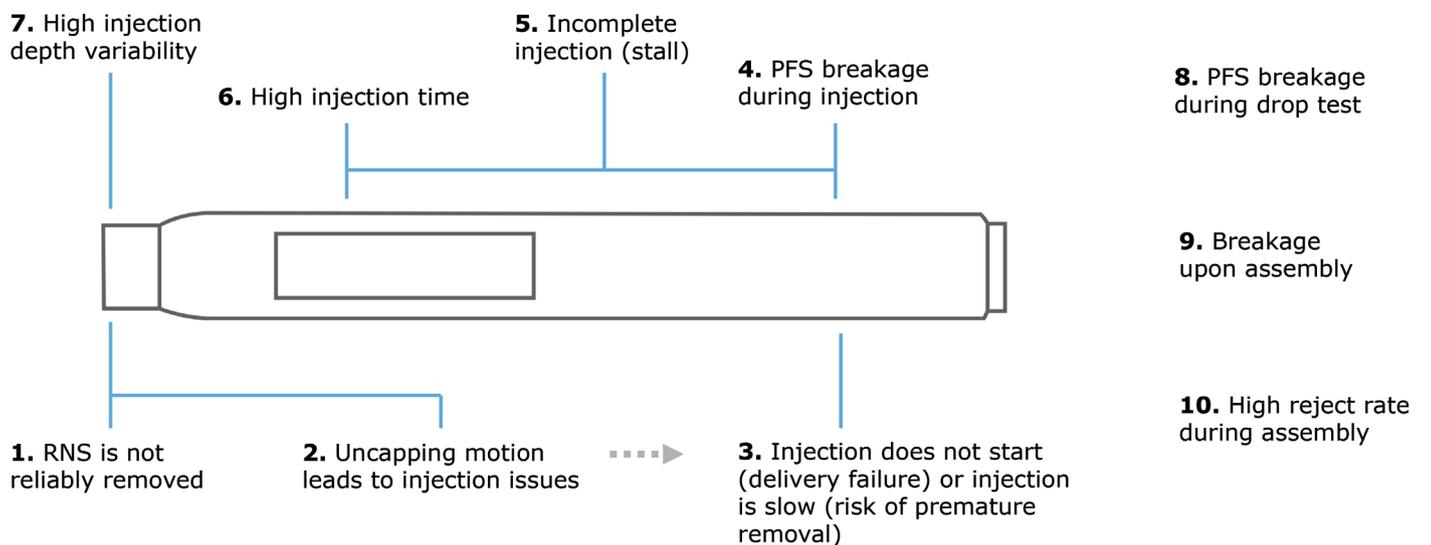


Figure 7: Most common challenges encountered with non-integrated components from different suppliers for auto-injectors.

the prefilled syringe team, to evaluate needle length variability and methods of controlling this dimension.

With the BD Physioject™ system, BD has addressed needle depth variability and conducted clinical studies to show how injection with BD Physioject™ compares to injection with a syringe alone. These studies provide evidence of more predictable clinical outcomes with BD's integrated system.

According to Fabien Dubuc, Platform Leader for Auto-Injectors with BD Intevia™, the team went a step further to optimise the system. They set a goal to eliminate the variability of requiring a skin pinch upon injection, simplifying the process for the patient. BD's ability to tightly control variability of components enables consistent targeting of the subcutaneous space. Preclinical studies have demonstrated that, without the use of a skin patch, BD can reliably control injection depth, greatly improving the injection experience.

Primary Container Defects

Limitation of a non-integrated system: Like needle extension, component

dimensional variability (e.g. prefilled syringe variability) is not always well accounted for in the design of the auto-injector assembly process. Higher reject rates and possible primary container breakage during assembly may occur as a result.

Integrated system solution: With BD's clear vision on detailed, proprietary prefilled syringe component specifications, critical dimensions to assembly which incorporate both BD Physioject™ and prefilled syringes are accounted for within the assembly process design. In an ISO 11608 drop test (1 m drop) study comparing BD Physioject™ with one of the most commonly marketed disposable auto-injectors, BD Physioject™ outperformed the comparator auto-injector in terms of prefilled syringe breakages and successful complete injections (Figure 8).

BD provides guidance for system assembly, ensuring that the process works smoothly with both the secondary delivery system and primary container, reducing the need for troubleshooting or other workarounds.

BD LIBERTAS™ EXAMPLE

Another example of where a systems integration approach adds value is the tolerance stack-up analysis conducted to design the BD Libertas™ wearable injector for high-scale production.

For example, to establish the axial clearance between the primary container and device flow path, an analysis of design parameters and geometric tolerances on nine dimensions was performed to ensure the resulting device's functional performance.

This approach to development enabled identification of critical inputs from a systems performance perspective and yielded a database of system specifications. This database houses hundreds of geometric tolerance stack-up chains that comprise system specifications and enabled a comprehensive understanding of how the device components, as a well integrated system, result in a high performing combination product: the BD Libertas™ wearable injector.

CONCLUSION

With a long history and expertise in combination products, BD is applying its knowledge to current needs in product development. The growing complexities and regulatory rigour of combination products has called for increasingly innovative delivery systems. BD's integrated systems offer a means to incorporate already existing world-class technologies with novel secondary delivery systems to provide complete systems that meet the evolving needs of pharmaceutical manufacturers.

Combined with BD's continuous process and service improvements, BD integrated solutions are designed to mitigate system performance risks, facilitate cost savings and prevent launch timeline delays to help pharmaceutical companies succeed in bringing their drug-device combination products to market and achieve commercial success.

BD Intevia™ and BD Libertas™ are products in development; some statements made are subject to a variety of risks and uncertainties. The combination products and the claims are subject to regulatory approval.

BD and the BD Logo are trademarks of Becton, Dickinson and Company.

Number of drops to break a prefilled syringe inside an auto-injector

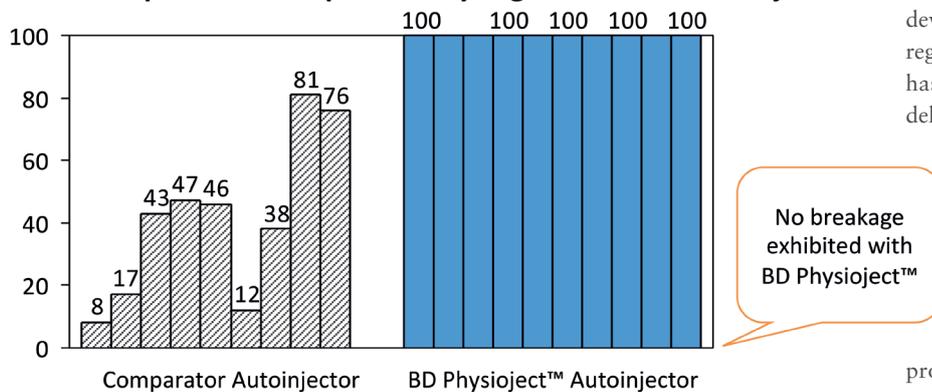


Figure 8: Comparison of auto-injectors with 1.0 mL prefilled syringes, filled with water. The same type of syringe was used inside all auto-injectors tested. Each bar represents one auto-injector. Auto-injectors were dropped a maximum of 100 times, or until prefilled syringe exhibited breakage. All BD Physioject™ samples confirmed intact by X-ray analysis. (BD internal study.)

ABOUT THE AUTHOR

Theresa Bankston, PhD, leads the Technical Services group for BD Medical – Pharmaceutical Systems that is responsible for providing technical support, solutions and services around delivery systems for injectable drug therapies. She has over 15 years of combined experience in the pharmaceutical and medical device industries. Her areas of expertise include process chemistry and engineering development, analytical method development and drug-container integration science. Theresa received her BS in Biochemistry from Florida State University and her doctorate in Chemical Engineering from the University of Virginia (NH, US), and a Bachelors' degree in Psychology from Boston College (MA, US).



THE DIFFERENCE OF **ONE** DRUG DELIVERED

FOR BETTER TREATMENT OF CHRONIC DISEASES. Across the healthcare continuum, BD is an industry leader in parenteral delivery devices that help health systems treat chronic diseases. We not only continually advance clinically proven, prefilled drug delivery systems, we do so with a vision to help healthcare providers gain better understanding of how patients self-inject their chronic disease therapies outside the healthcare setting. This is why we partner with leading pharmaceutical and biotech companies worldwide to develop digitally connected self-injection devices—including wearable injectors and autoinjectors—to capture valuable data that can be shared with caregivers. Discover how BD brings new ideas and solutions to customers, and new ways to help patients be healthy and safe. **Discover the new BD.**



BD Libertas™ wearable injector



BD Intevia™ disposable autoinjector



BD Physioject™ disposable autoinjector

Learn more at bd.com/Discover-BD1

BD Libertas™ wearable injector, and BD Intevia™ disposable autoinjector are products in development; some statements made are subject to a variety of risks and uncertainty.

© 2017 BD. BD and the BD Logo are trademarks of Becton, Dickinson and Company. BDPS24704

